

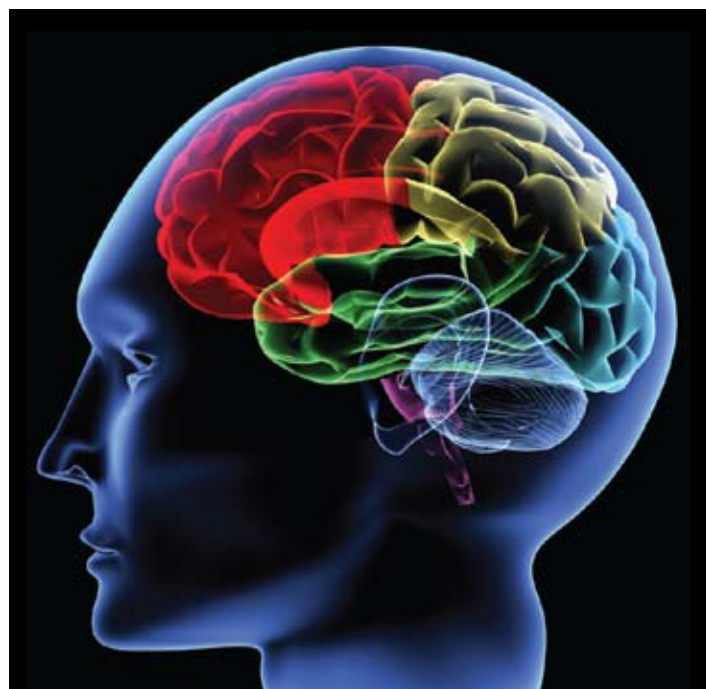
A Primer on the Neurological Complications of Sjögren's

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Patients with neurological manifestations of Sjögren's Syndrome can face a lonely and isolating journey. The neurological complications of Sjögren's are myriad, ranging from cognitive difficulties to burning toes and feet. Unfortunately, subtle neurologic symptoms often are overlooked by physicians. This can lead to a disenfranchising experience where devastating neurologic complications are marginalized by the medical profession. Progression of neurologic Sjögren's Syndrome can have a traumatic impact on patients. However, the symptoms of neurological Sjögren's can be gratifyingly responsive to different therapeutic regimens. A rational diagnostic approach can lead to the alleviation of pain and greatly improve quality of life.

This year at Johns Hopkins, I have started a Neurology-Rheumatology Clinic devoted to care of patients with neurological complications of Sjögren's disease. My background is that I am both a neurologist and rheumatologist. This cross-disciplinary perspective has afforded insight into the challenges that may afflict patients with neurological complications of Sjögren's who may be caught between the crosswinds of discrepant opinions between neurologists and rheumatologists. Furthermore, the perspective of either neurologists or rheumatologists may not adequately capture the scope and complexity of problems uniquely affecting patients with neurologic Sjögren's.

Below, I share my diagnostic strategy in evaluating and treating patients with neurological manifestations of Sjögren's disease. The art of a careful history and exam should sharpen the



diagnostic process and help guide further decisions. I emphasize the limitations of current blood and invasive tests. Both rheumatologists and neurologists are often guilty of excessive faith in blood tests and nerve-conduction tests. I illustrate that 'negative' tests may reflect the limitations of an imperfect test and should not substitute for clinical judgment.

Introduction to the nervous system

Fundamentally, the biologic nervous system is divided into two anatomic compartments:

The 'Central Nervous System' – or CNS – includes the brain and the spinal cord.

The 'Peripheral Nervous System' – or PNS – includes larger and smaller nerves, connecting muscles to the spinal cord.

Sjögren's Syndrome can cause inflammation and damage to the CNS and PNS. Below is a review of diagnostic strategies in approaching patients with CNS and PNS complications of Sjögren's. It emphasizes that diagnostic strategies should be tailored toward salient symptoms and mechanisms.

Peripheral neuropathy of Sjögren's Syndrome

What is neuropathy?

Neuropathy, which means inflammation and/or damage to the peripheral nerves, can be an agonizing source of distress for patients with Sjögren's. Neuropathy can cause various symptoms from 'numbness' to 'coldness'. At its most severe, neuropathy has been described as 'burning', 'lancinating' or 'feeling like my skin is on fire'. Neuropathy also can cause weakness and clumsiness.

How do doctors diagnose neuropathy?

The first step is to take a careful history and do a physical examination. The pattern and description of symptoms, which may include pain and weakness, may suggest damage to the peripheral nerves. A neurological examination is crucial in providing objective evidence of peripheral neuropathy. Weakness may be present, which is typically greater in the toes and fingers than in the larger muscle groups of the arms and legs. Physicians may test one's reflexes. Whereas a reflex hammer should elicit emphatic lurches of arms and legs, patients with neuropathy may not have any reflexes. Lastly, physicians may test the ability to appreciate temperature, a sharp pin, and vibration. If the neurological examination confirms a peripheral neuropathy, then the physician may order a nerve-conduction test, looking at the integrity of nerves and muscles.

My experience at the Johns Hopkins Neurology-Rheumatology Clinic is that patients with neuropathy and Sjögren's Syndrome often undergo an incomplete diagnostic evaluation. Following is a review of some pitfalls in the diagnostic evaluation of Sjögren's neuropathy.

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Why is neuropathy under-diagnosed or under-treated in Sjögren's Syndrome?

1. Sjögren's may uniquely target nerves which are not tested on normal nerve-conduction tests.

Neuropathy can target nerves of larger and smaller caliber, respectively referred to as a 'large-fiber' neuropathy versus a 'small-fiber' neuropathy. Symptoms of large fiber neuropathy include weakness and poorly localizable numbness and are associated with abnormalities on nerve-conduction tests.

In contrast, patients with small-fiber neuropathy may have more dramatic and piercing symptoms of pain, burning, and prickling, even without weakness. The nerve-conduction test is only sensitive to inflammation and destruction of large-fiber nerves. Nerve-conduction tests are not capable of detecting any abnormalities in the smallest-caliber nerves. In the context of these 'normal' nerve-conduction tests, rheumatologists frequently and mistakenly conclude that despite symptoms of small-fiber neuropathy, there is no objective evidence of neuropathy. The suffering of patients is amplified by the intimation that there is no real or concrete evidence of nerve damage. This is an example of not recognizing the limitations of medical technology, and putting more faith in a limited test instead of the voice and heart of the patient.

At the Johns Hopkins Neurology-Rheumatology Clinic we routinely order skin biopsies to help diagnose and treat symptoms of small-fiber neuropathy in Sjögren's patients and others who have normal nerve-conduction tests. The skin biopsy requires a negligible incision, with no scarring, and only needs a small band-aid.

Conclusion

In the context of symptoms which may suggest a small fiber neuropathy, a 'normal' nerve-conduction test can support rather than refute the clinical impression of a neuropathy. Patients with complaints of burning or prickling pain in the toes or feet should be evaluated by skin biopsy.

2. Sjögren's patients may lack definitive blood tests.

Sjögren's Syndrome is an example of an autoimmune syndrome. In autoimmune disorders, the immune system, which normally protects the body from infection and cancers, turns into a traitor and starts waging war against crucial organs. In addition to the nervous system, areas of the body which may be targeted in Sjögren's Syndrome include the eye, the lung, the heart, the kidney, and the joints. Many patients with Sjögren's Syndrome have abnormal autoantibodies, which are proteins that destroy normal appearing cells. Some examples of abnormal autoantibodies in Sjögren's Syndrome are anti-Ro (or SS-A antibodies) and anti-La (or SS-B antibodies).

However, more than 50% of patients with neurological manifestations of Sjögren's may not have abnormal autoantibodies. Unfortunately, this important statistic is often overlooked by neurologists. Therefore, when confronted with negative autoantibodies, many neurologists inappropriately and erroneously terminate a workup for neuropathy, even when there is a compelling history of Sjögren's.

Accordingly, in patients who have neuropathy and compelling glandular symptoms of dry eyes and dry mouth, negative blood tests for SS-A and SS B antibodies do not exclude the diagnosis of Sjögren's Syndrome. In the context of sicca symptoms, further diagnostic studies are warranted, including a Schirmer's test and a minor salivary gland biopsy.

Conclusion

Neurologists should recognize that approximately 50% of patients with Sjögren's Syndrome may not have specific autoantibodies and blood tests. Termination of diagnostic evaluation for Sjögren's Syndrome when confronted with negative SS-A and SS-B antibodies is premature. All patients with unexplained neuropathy and symptoms of dry eye and/or dry mouth in the presence of 'negative autoantibodies' should undergo a lip biopsy for confirmation of Sjögren's Syndrome. Any workup terminated on the basis of a blood test may be premature and may result in ongoing and under-treated symptoms of neuropathy.

What are other types of neuropathy that can occur in Sjögren's Syndrome?

1. Autonomic neuropathy

Sjögren's Syndrome can cause damage to nerves that regulate the coordination of heartbeat, respiration, and gastric motility. This is called an 'autonomic neuropathy'. Examples of symptoms include lightheadedness when standing, decreased or increased sweating, and feeling full despite eating small meals. The diagnosis of autonomic neuropathy should be made by a neuromuscular specialist.

2. Trigeminal neuralgia and glossopharyngeal neuralgia

Sjögren's Syndrome can cause numbness or burning of the face, called 'trigeminal neuralgia'. Pain in the back of the throat, which may worsen while swallowing, is called 'glossopharyngeal neuralgia'. Patients with trigeminal or glossopharyngeal neuralgia may have agonizing mouth and facial pain. These neuropathies may co-exist with other neuropathies in different parts of the body. For example, up to 20% of patients with a 'small-fiber' neuropathy may also have trigeminal neuropathy.

Medicines which may help alleviate symptoms in small-fiber neuropathy also may have efficacy in trigeminal neuralgia. Such medications may include a class of agents which are typically used to treat seizures, including neurontin, topamax, and lycrica. In seizure disorders paroxysmal and irregular bursts of electrical activity in brain nerves may lead to propagation of seizures. Similarly, in Sjögren's neuropathy irritative electrical signals produced by nerves in the skin instead of the brain may similarly contribute to pain. Just as anti-seizure medicines can dampen electrical activity of brain cells, the dampening of electrical activity produced by pain-fibers may ameliorate burning pain. Consultation with a neurologist who is well-versed in both dosages and side-effects of anti-seizure medicines is crucial. It is important to note that use of these symptomatic medications does not target the neuron-inflammation which may be contributing to neuropathy. In such cases, judicious use of immunosuppressant medications should be considered.

3. Mononeuritis multiplex

More severe patterns of weakness or clumsiness may cause weakness or paralysis of different muscles. This is called 'mononeuritis multiplex'. These more cataclysmic episodes of numbness or weakness necessitate a thorough diagnostic evaluation by nerve-conduction tests and often by biopsy of nerves and/or muscles. Mononeuritis multiplex occurs when there is inflammation of small blood-vessels. The muscles and nerves nourished by such blood vessels may be deprived of oxygen and nutrients — similar to a 'stroke of the nervous system'. In such cases, ameliorating symptoms of pain is not sufficient — immunosuppressant therapy is always warranted in cases of mononeuritis multiplex.

The pace of recovery from mononeuritis multiplex can be frustratingly slow. In some cases it may be difficult to determine

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whether a slow pace of recovery is due to ongoing and ineffectively treated inflammation or if it is just a manifestation of the slow process of healing and 'rewiring'. In such cases repeat nerve-conduction tests may be important. Consultation with a neurologist and/or rheumatologist experienced in treating vasculitis is important. Immunosuppressant medications which may be used in the pattern of mononeuritis multiplex include cyclophosphamide and imuran as well as prednisone.

How is the neuropathy of Sjögren's treated?

In general, a neurologist and/or rheumatologist must determine the 'pattern' of neuropathy (i.e. mononeuritis multiplex versus 'small-fiber' neuropathy). Distinguishing between these patterns is of paramount importance, because of distinguishing mechanisms which may necessitate different therapeutic strategies. The pain of neuropathy can be especially severe and may require different analgesics and anti-seizure medications. However, symptomatic treatment of pain should not preclude the institution of medications to dampen the immune-system when there is evidence of ongoing neuroinflammation.

CNS or central nervous system complications of Sjögren's Syndrome

Myelitis

Patients with Sjögren's Syndrome may have 'myelitis', which is inflammation of the spinal cord. Myelitis can cause weakness, numbness, and difficulty with urination and/or defecation. Myelitis can present quickly (i.e. within hours); however, symptoms due to inflammation of the spinal cord may evolve more slowly, progressing over weeks or months. This slower progression may be difficult to distinguish from multiple sclerosis (MS). Unfortunately, patients with myelitis and Sjögren's Syndrome can be misdiagnosed with MS. Appropriate tests, which may include spinal tap and MRI of the brain/spinal cord, can lead to diagnostic clarity. The importance of accurately distinguishing between multiple sclerosis and Sjögren's Syndrome is of paramount importance. MS and Sjögren's have completely different treatments. The approved treatments for MS are ineffective for Sjögren's Syndrome and may actually lead to 'flares' or worsening of Sjögren's.

Patients with Sjögren's Syndrome may have another autoimmune disorder called 'Devic's syndrome', or 'neuromyelitis optica'. Neuromyelitis optica (NMO) causes inflammation of the nerves connecting the eye to the brain, or 'optic neuritis', as well as myelitis. The pattern of myelitis which can occur in neuromyelitis optica is much different than multiple sclerosis. Typically, the myelitis in NMO is more severe, causing severe weakness, and may cause future relapses.

Again, the treatment for neuromyelitis optica is much different than MS. Patients with Sjögren's Syndrome who are diagnosed with MS need to be skeptical about receiving these dual diagnoses. Below, I offer some helpful hints, which may especially cast doubt on the diagnosis of MS.

Red flags for a diagnosis of neuromyelitis optica

Answering 'yes' to the questions below should especially raise consideration for the diagnosis of neuromyelitis optica:

- Have episodes of myelitis been especially severe. (i.e. associated with inability to lift the arms or legs in the air)?
- Have there been multiple relapses?
- Have episodes of myelitis been associated with 'optic neuritis', inflammation of the nerves connecting the eye to the brain?
- Have MRIs of the spine shown inflammation which extends beyond three 'back bones' or vertebral bodies?

Any patient with Sjögren's Syndrome, a history of myelitis, and answering 'yes' to the above questions should have a blood test which may assist in the diagnosis of neuromyelitis optica. The name of this blood test is the NMO-IgG antibody and is performed at the Mayo Clinic. It detects neuromyelitis optica in 70 percent of cases. This means that it is not a perfect blood test and will be negative in 30 percent of cases. In such cases, consultation with a neurologist with training in neuroimmunological disease is crucial.

Red flags against a diagnosis of primary-progressive multiple sclerosis

Multiple sclerosis is not a single disease but has different presentations with different tempos. The most common type of MS is called 'relapsing-remitting' MS and is punctuated by episodes of unequivocal deterioration (called 'flares') versus periods of clear improvement and quiescent disease. However, a different type of MS may be confused with Sjögren's Syndrome. This pattern is called 'primary-progressive' MS. In such cases the crescendos of worsening and improvement typical of 'relapsing-remitting' MS are not evident. Instead, there may be a slower and more gradual period of deterioration, reflecting inflammation and damage in the spine (i.e. progressive myelitis).

Patients with Sjögren's Syndrome who receive a dual diagnosis of primary-progressive MS need to be especially vigilant about diagnostic misimpression! Specifically, there is no effective treatment for primary-progressive MS. Any patient with Sjögren's who receives a diagnosis of primary-progressive MS deserves a trial of immunosuppressant medication which may be helpful if progressive myelitis is occurring because of Sjögren's Syndrome.

Are there any ways of distinguishing between primary-progressive MS and the progressive myelitis because of Sjögren's Syndrome? We are currently exploring different strategies for improved diagnostic discrimination. It is often difficult to distinguish between primary-progressive MS and Sjögren's disease. Patients with Sjögren's may have less brain disease on MRI compared to patients with primary-progressive MS. In addition, patients with Sjögren's may have lesser amounts of protein in the spinal fluid, called 'oligoclonal' bands. Therefore, any Sjögren's patients with a diagnosis of primary-progressive MS need to have brain MRIs as well as a spinal tap. However, these tests do not exhaustively cover the subtle clinical clues which may help in diagnostic discrimination. In such cases, consultation with a neuroimmunologist is essential.

Conclusions

The most common CNS complications of Sjögren's Syndrome include myelitis and optic neuritis, which are syndromes that can occur in MS. Because of this symptomatic overlap, patients with Sjögren's may erroneously receive a diagnosis of MS. Because the treatments for MS are not only ineffective for Sjögren's but may actually precipitate flares of Sjögren's, accurate distinction between MS and Sjögren's Syndrome is crucial. When the myelitis is particularly severe, associated with optic neuritis, or involves extensive regions of the spine, then the diagnosis of Neuromyelitis Optica should be considered. Spinal taps and brain MRIs may help in the distinction between primary-progressive MS and Sjögren's Syndrome. All patients with myelitis in the context of Sjögren's Syndrome deserve a trial of immunosuppressant therapy.

Patients with neurological complications of Sjögren's Syndrome should feel free to contact Dr. Birnbaum by email at jbirnba2@jhmi.edu.

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